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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 12-NOV-1998

SUBJECT: ID#98ID0040. SECTION 18 EXEMPTION FOR THE USE OF
DIFENOCONAZOLE ON SWEET CORN SEED IN IDAHO.

DP Barcode: 249122	PRAT Case#: 290461
Submission #: S547588	Caswell#: 955
Chemical#: 128847	Class: Fungicide
Trade Name: Dividend™ 3FS	40 CFR: 180.503
EPA Reg#: 100-740	

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INTRODUCTION

The Idaho Department of Agriculture is proposing a section 18 exemption for the use of difenoconazole on sweet corn for control of fungal pathogens (Penicillium SPP, Pythium SPP, and Fusarium SPP) infesting seed corn. This is the first Section 18 request for this use. The proposed program will entail the application of a maximum of 390 gallons [1000 lbs ai] on no more than 10 million pounds of sweet corn seed statewide from September 1, 1998 to September 1, 1999.

SUMMARY

Dividend™ 3FS is a Novartis seed treatment product containing 32.8 percent of the active ingredient difenoconazole. This product is exclusively used for commercial seed treatment. It is important to note that the label specifically prohibits using this product in an agricultural setting. Therefore, there is no post-application exposure to the farm workers. In addition, there are no residential uses currently registered for difenoconazole.

Based on the low toxicity, the application rate of 0.05 fl.oz. per 100 lbs seed, and the limited number of applications, there is minimal concern for potential inhalation exposure. A 75 percent dermal penetration factor was applied to the route to route extrapolation for dermal risk assessment. The subgroup population of interest was determined to be females (13+) for acute dietary. No acute dietary assessment was performed for the general population due to the fact that there were no observable toxic effects in the oral toxicological studies. Residues of difenoconazole are not expected to exceed 0.1 ppm in/on corn, sweet (K + CWHR), corn, sweet, forage, or corn, sweet, stover as a result of this Section 18 use. Time-limited tolerances for the residues of difenoconazole should be established at these levels. Occupational exposure and aggregate risk estimates do not exceed HED's level of concern. The agency recommends for the issuance of this Section 18 exemption for the use of difenoconazole on sweet corn seed in the State of Idaho.

TOXICOLOGICAL ENDPOINTS

1. Dietary

- a. **Acute RfD.** 0.25 mg/kg/day. For acute dietary risk assessment, the Hazard Identification Assessment Review Committee (HIARC) recommended use of the NOAEL of 25 mg/kg/day with an uncertainty factor of 100, based on increases in post-implantation loss and resorption and decreases in fetal body weight and decreases in body weight gains and food consumption in dams at the LOAEL of 75 mg/kg/day, from the developmental study in rabbits (MRID# 42090017). This risk assessment will evaluate acute dietary risk to females 13+ years, the population subgroup of concern (Memo, A. Kocialski and J. Rowland, 9/25/98).

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF}} = \text{mg/kg/day}$$

There was no acute RfD determined for the general population including infants and children.

- b. **Chronic Toxicity.** RfD = 0.01 mg/kg/day. The Reference Dose (RfD) was established based on a chronic-feeding/oncogenicity study in rats in (MRID# 42090019;20) with a NOAEL of 0.96 mg/kg/day and an uncertainty factor of 100 based on cumulative decreases in body weight gains at the LOAEL of 24.0 mg/kg/day (Memo, A. Kocialski and J. Rowland, 9/25/98).

2. Non-dietary

- a. **Short-Term Toxicity.** For short-term Margin of Exposure (MOE) calculations, the HIARC recommended use of the developmental NOAEL of **25 mg/kg/day** from the developmental rabbit study (MRID# 42090017) with a dermal absorption factor adjustment of 75%. At the LOAEL of **75 mg/kg/day**, there were increased post-implantation losses and resorptions per dose and a significant decrease in fetal body weight, and decrease in body weight gains and food consumption in dams (Memo, A. Kocialski and J. Rowland, 9/25/98).
- b. **Intermediate-Term Toxicity.** For intermediate-term MOE calculations, the HIARC recommended use of the NOAEL of **1.25 mg/kg/day** from the two generation study in rats (MRID# 42090018). At the LOAEL of **12.5 mg/kg/day**, there were decreased pup weights (Memo, A. Kocialski and J. Rowland, 9/25/98).
- c. **Chronic Toxicity.** The HIARC determined that a chronic toxicity endpoint and risk assessment for difenoconazole is not required for workers for this use (Memo, A. Kocialski and J. Rowland, 9/25/98).
- d. **Dermal Penetration.** Dermal penetration = 75%. For MOE calculations, a developmental toxicity study was used, in conjunction with a 21 day dermal rabbit study with the resulting recommendation being that a 75% dermal absorption factor be applied to the route to route extrapolation for dermal risk assessments. The dermal absorption factor of 75% for dermal exposure should be used and converted to equivalent oral dose for the dermal exposure and compared to the oral NOAEL (Memo, A. Kocialski and J. Rowland, 9/25/98).

CANCER

Difenoconazole has been classified as a **Group C possible carcinogen** chemical by the Cancer Peer Review Committee (CPRC). The Committee recommended using the margin of exposure (MOE) approach (Memo, Jess Rowland and Esther Rinde, 7/24/94).

EXPOSURES AND RISKS

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor and/or outdoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

1. *From Food and Feed Uses:*

Time-limited tolerances for residues of difenoconazole [(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1H-1,2,4-triazole for wheat commodities has been granted and a permanent tolerance is currently being evaluated by EPA. The time-limited tolerances for

wheat hay, straw and grain are 0.05 ppm, 0.05 ppm and 0.01 ppm, respectively. This time-limited wheat tolerance will expire 12/31/98. Registration for barley is currently under review by the Agency. In addition, Novartis has established twelve sweet corn trials utilizing defenoconazole treated seeds and intends to pursue a full Section 3 registration for corn seed treatment, (submitting a petition to the Agency in the fourth quarter of 1999).

a. Acute Risk

An acute dietary risk assessment is required for difenoconazole. The NOAEL of **25** mg/kg/day is based on post-implantation loss and resorption/dose and a significant decrease in fetal weight at **75** mg/kg/day during days 7 and 19 of gestation. The acute RfD is **0.25** mg/kg. HED's detailed acute analysis estimated the distribution of single-day exposures for the females (13+ years old). A dose and endpoint were not selected for the general U.S. population and infants and children because there were no effects observed in oral toxicological studies including maternal toxicity in the developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure). The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. Each analysis assumes uniform distribution of difenoconazole in the commodity supply.

The acute exposure analysis for female (13+) subgroup was performed using tolerance level residues and **100** percent crop treated (Attachment 1 runs dated 10/19/98).

Total from new and published tolerances at the 95th percentile are listed in Table 1.

Table 1: Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
Females (13+/pregnant/not nursing)	0.000913	<1
Females (13+/nursing)	0.001079	<1
Females(13-19 yrs/not preg. or nursing)	0.000941	<1
Females (20+ years/not preg. or nursing)	0.000804	<1
Females (13-50 years)	0.000869	<1

HED does not consider the acute dietary risk to exceed the level of concern.

b. Chronic Risk

A chronic dietary risk assessment is required for difenoconazole. The RfD used for the chronic dietary analysis for difenoconazole is **0.01** mg/kg bwt/day.

Chronic dietary exposure estimates (DEEM™) for difenoconazole are summarized in Attachment 1 (runs dated 10/19/98). The chronic DEEM™ used mean consumption (3 day average) and tolerances for all sweet corn seed commodities. Since the FQPA factor was removed from all population groups, the RfD used in this analysis does not incorporate a safety factor. The results are listed in Table 2.

Table 2: Chronic Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
U.S. Population (48 states)	0.000558	5.6
Non-Hispanic other than black or white	0.000602	6.0
All infants (< 1 year)	0.000741	7.4
Nursing Infants (< 1 year old)	0.000274	2.7
Non-Nursing Infants (< 1 year old)	0.000938	9.4
Children (1-6 years old)	0.001368	13.7
Children (7-12 years old)	0.000878	8.8
Females (13+/-nursing)	0.000504	5.0
Males (13-19 years)	0.000603	6.0

HED does not consider the chronic dietary risk to exceed the level of concern.

c. Cancer Risk

Using the NOAEL of 4.7 mg/kg/day determined by HIARC, the dietary cancer MOE was determined to be **8400** for the U.S. population. Since the calculated cancer MOE is well above 100, the cancer risk does not exceed HED's level of concern (Memo, A. Kocalski and J. Rowland, 9/25/98).

2. From Drinking Water:

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for difenoconazole at this time. The Environmental Fate and Effects Division (EFED) provided ground and surface water exposure estimates for use on seed (Memo, J. Hetrick, 10/28/98).

The drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since difenoconazole is used solely as a fungicide on the seed coat of small grains to control soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. These modeling assumptions are expected to yield highly conservative estimates for difenoconazole concentrations in drinking water.

EFED recommended that the registrant submit aerobic soil metabolism and batch equilibrium data to provide a limited understanding on the fate and transport of difenoconazole. Additional environmental fate data (e.g., terrestrial field dissipation) may be needed to confirm routes and rates of dissipation under actual use conditions. (Memo, J. Hetrick, 10/28/98)

a. Ground Water (tiered assessment)

In order to conduct Tier 1 modeling for difenoconazole, the following assumptions were made: 1.) Complete dissociation of difenoconazole from the seed coat is assumed; and 2.) Difenoconazole is persistent ($t_{1/2} = 365$ days) and mobile ($K_{oc} = 0.0$) in terrestrial and aquatic environments. The Tier 1 SCI-GROW modeling predicts that ground water concentrations of difenoconazole is not likely to exceed 12.08 $\mu\text{g/L}$ (Memo, J. Hetrick, 10/28/98).

b. Surface Water (tiered assessment)

Surface water estimates were made using the GENEEC model. The maximum difenoconazole application rate is 0.01498 lbs ai/A, which accounts for a maximum wheat application rate of 60 lbs seed/A treated with 11 g ai/100 kg seed. Tier 1 GENEEC modeling for the maximum application rate of Dividend 0.31 FS (EPA Reg. No. 100-778) indicates the maximum (acute endpoint) and 56 day average (chronic endpoint) concentrations of difenoconazole in surface water are not likely to exceed 0.837 and 0.835 $\mu\text{g/L}$, respectively (Memo, J. Hetrick, 10/28/98).

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

OPP has calculated DWLOCs for acute exposure to difenoconazole in drinking water for the females (13+ years old, nursing) to be **7500 ppb**. For chronic (non-cancer), the DWLOCs are **330** and **97 ppb** for U.S. population, nursing infants less than 1 year old, respectively. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™ analysis) was subtracted from the RfD to obtain the acceptable acute exposure to difenoconazole in drinking water. To calculate the DWLOC for chronic (non-cancer, cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the RfD to

obtain the acceptable chronic (non-cancer) exposure to difenoconazole in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures.

Calculation:

$$DWLOC_{\text{chronic or acute}} (\mu\text{g/L}) = \frac{(\text{chronic or acute}) \text{ water exposure (mg/kg/day)} \times (\text{body weight})}{\text{consumption (L)} \times 10^{-3} \text{ mg}/\mu\text{g}}$$

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface and ground water to back-calculated DWLOCs for difenoconazole. These DWLOCs were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of difenoconazole are derived from water quality models that use conservative assumptions (health protective) regarding the pesticide transport from the point of application to surface and ground waters. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate risk assessment process.

HED determined that the maximum estimated concentrations of difenoconazole in surface and/or ground water is not likely to exceed OPP's DWLOCs for difenoconazole as a contribution to acute and chronic aggregate exposure. OPP concludes with reasonable certainty that residues of difenoconazole in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

3. ***Occupational and Residential Exposure and Risk Assessment/Characterization:***

a. **Occupational and Residential Exposure**

i. **Summary of Use Patterns and Formulations**

This occupational risk assessment addresses the use of the 32.8% 3FS formulation of difenoconazole. The petitioner (Idaho Department of Agriculture) proposes an application rate of 0.01 pounds active ingredient (a.i.) per 100 pounds of seed for a maximum of 10 million pounds of sweet corn seed.

Difenoconazole under this FIFRA Section 18 is used as a commercial-use fungicide used to treat fungal pathogens on sweet corn seed. Commercial seed treatment is comprised of three operations; mixing, bagging, and bag

sewing. These work functions are described further in the **Seed Treatment Exposure and Assumptions Section** of this report.

For agricultural workers, exposure will be limited. This is due to the fact that the planting of corn seed is done mechanically. Therefore, exposure will consist of the workers opening the treated seed bags and emptying the contents into the application equipment.

Difenoconazole is not currently registered for any residential uses. Therefore, no non-dietary, non-occupational exposure is anticipated.

ii. Seed Treatment Exposures and Assumptions

In a typical commercial seed treatment facility, (according to Mr. Russell of the Novartis Seed Treatment Facility (personal communication, 10/98)), treatment is usually done using automatic, computerized equipment. In the case of difenoconazole, due to the small amount used, the fungicide is manually added (via graduated cylinder). Baggers and bag sewers are also part of the operation. The work area is supplied with aspirators to minimize inhalation exposure. For difenoconazole, this activity is usually performed five days a week for three weeks, three times per year.

HED's exposure assessment is based on the assumptions in Table 3.

Table 3. Assumptions for Commercial Handler Exposure Assessments

Factors	Quantities/Units	Source
Crop to be treated	sweet corn seed	Section 18 exemption letter
Pests	fungal pathogens	Section 18 exemption letter
Manufacturer	Novartis Crop Protection, Inc.	label
Seed-treatment workers	60 kg	EPA default for females
Application rate for commercial seed treatment.	0.01 lb ai/100 lbs seed	Section 18 exemption letter
Application Type	commercial mist-type seed treatment	label
Days worked per week	2-3	Mr. Russell, Novartis Seed Treatment Facility
Weeks worked per year	9	Mr. Russell, Novartis Seed Treatment Facility
Personal protective equipment (PPE)	none	label

HED has very limited data for seed treatment scenarios. These exposure estimates for commercial seed treaters are based on data from a study entitled **Worker exposure to Apron Flowable while treating seed commercially** submitted in support of MAXIM 4FS (Ciba-Geigy, 1993). This study was reviewed by HED in August 1994 (Memo, B. Kitchens, 8/23/94). The following table expresses all assumptions taken from this

study and used in calculating commercial seed treater exposure.

Table 4: Assumptions taken from Study: Worker Exposure to Apron Flowable while treating seeds commercially

Worker involved in commercial seed treatment	Mixer, Bagger, Bag Sewer	
Bag size	50 lbs	
Bags produced per hour	250	
Hours worked per day	8	
Personal Protective Equipment worn by Mixer	Chemical apron, gloves, goggles	
Personal Protective Equipment worn by Bagger and Bag Sewer	Long sleeved shirt, long pants	
Seed treated per day	100,000 lbs	
Maximum Mixer unit exposures (mg/kg ai)	Dermal: 0.0610	Inhalation: 0.000775
Maximum Bag sewer unit exposures (mg/kg ai)	Dermal: 0.0346	Inhalation :0.0056
Maximum Bagger unit exposures (mg/kg ai)	Dermal: 0.0182	Inhalation: 0.000518

This study determined the amount of active ingredient that mixer/operators, baggers and bag sewers are exposed to during the commercial treatment of seed. Also, it is the only study available that is comparable for a commercial seed treatment operations. Fundamentally, the study and proposed use are the same; both are seed treatments, with the same type of formulation applied by the same equipment for commercial use.

iii. Commercial Seed Treater Exposure Assessment Formulas and Exposure Tables

Table 5 summarizes the HED/RAB1 estimates for exposure for commercial seed treaters including mixer/loaders, baggers, and bag sewers. Based on the use-pattern, only short-term exposures are expected from the proposed use.

Table 5. Seed Treatment Exposure to Dividend™ 3FS fungicide*

Job Function	Average Dermal Daily Dose (ADD) for Dividend™ 3FS mg ai/kg bw/day	Average Inhalation Daily Dose (ADD) for Dividend™ 3FS mg ai/kg bw/day	Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE
Mixer/Operator	0.0035	0.000059	7213	0.00022	2.2 x 10 ⁴
Bag Sewers	0.0020	0.00050	12717	0.00015	3.2 x 10 ⁴
Bagger	0.0010	0.000039	24176	0.000066	7.1 x 10 ⁴

Equations:

$$\text{MOE (short-term dermal)} = \frac{\text{NOAEL (25 MG / KG / DAY)}}{\text{ADD}}$$

$$\text{ADD} = \left(\left(\left(\text{UNIT EXPOSURE} \left(\frac{\text{MG}}{\text{KG AI}} \right) \right) \times \left(\frac{1 \text{ KG}}{2.2 \text{ LBS}} \right) \times \left(\text{APPLICATION RATE} \left(\frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \right) \times 0.75 (\text{dermal absorption})$$

$$\times \left(\frac{\text{SEED}}{\text{BAG}} \right) \times \left(\frac{\text{BAGS}}{\text{HOUR}} \right) \times \left(\frac{\text{HOURS}}{\text{DAY}} \right) \times \left(\frac{1}{\text{BODY WEIGHT (KG)}} \right)$$

$$\text{LADD} = \text{ADD (inhalation \& dermal)} \times \left(\left(\frac{\text{Days Worked}}{\text{Week}} \right) \times \left(\frac{\text{Weeks Worked}}{\text{Year}} \right) \right) \times \left(\frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right)$$

$$\text{CANCER MOE} = \frac{\text{NOAEL (4.7 MG / KG / DAY)}}{\text{LADD}}$$

iv. Farm Worker Exposures and Assumptions

According to Mr. George Robinson from Idaho Department of Agriculture (personal communication, 10/98), the planting of corn seed is done mechanically. Therefore, the potential for agricultural worker (other than the mixer/loader scenario) exposure to difenoconazole is expected to be minimal.

PHED version 1.1 data was used to estimate exposure for mixer/loader workers opening and loading the bags of treated seed. Currently, PHED does not contain data on the specific scenario. Therefore, the closest possible match is GRANULAR OPEN MIXING. The 'no gloves' unit exposure was used as a conservative assumption due to lack of label PPE instructions. The quality of the dermal data is considered '**low confidence**' (ABC grade, low replicates, and poor grade quality of hand replicates). The quality of the inhalation data is considered '**high confidence**' (AB grade, high replicates). Consideration was also given to the fact that limited farm worker exposure is expected.

Typical corn-planting information, such as the number of acres planted per

day and the pounds of seed planted per acre, was also obtained from the Idaho Department of Agriculture (Mr. George Robinson). This information, considered in calculating exposures estimates, is listed below in Table 6.

Risk assessments will be done for the worst case scenario. In this case, the mixer/ loader scenario indicates the highest exposure activities for farm workers. Therefore, exposure estimates were only done for this group of farm workers, representing the highest possible exposure of all groups performing loading and planting of treated seeds.

Table 6: Farm Worker Exposure Assumptions

Scenario	Exposure	Unit Exposure (mg/lb ai)	Application Rate	Pounds seed /Acre	Acres /day	Body Weight (kg)
Mixer/ Loader	Dermal	0.0084	0.01 lbs ai/100 lbs seed	8	120	60
Mixer/ Loader	Inhalation	0.0017				
<u>Source</u>	- -	PHED 1.1 Granular open pour, no gloves	Label	ID Dept. of Agriculture	ID Dept. of Agriculture	Default for females

v. Farm Worker Exposure Assessment Formulas and Exposure Tables

In calculating Lifetime Average Daily Dose (LADD), it was assumed that the farm worker would plant 120 Acres per day with treated seed, three days per week for two weeks each year, for thirty-five years over a seventy-year lifespan. The exposure scenario is intended to represent commercial workers. Since the average corn farm is approximately 120 acres in size, most growers are able to manage planting themselves. Therefore, the estimates are considered conservative.

Table 7. Farm Worker Exposure to Dividend™ 3FS Treated Seeds

Job Function	Average Dermal Daily Dose (ADD) for Dividend™ 3FS mg ai/kg bw/day	Average Inhalation Daily Dose (ADD) for Dividend™ 3FS mg ai/kg bw/day	Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE
Mixer/Loader	0.000010	0.0000027	2.48×10^6	0.00000011	4.5×10^7

Equations:

$$\text{MOE}_{\text{(short-term dermal)}} = \frac{\text{NOAEL}(25 \text{ MG / KG / DAY})}{\text{ADD}}$$

$$\text{MIXER / LOADER: ADD} = \left(\left(\text{UNIT EXPOSURE} \left(\frac{\text{MG}}{\text{LB AI}} \right) \right) \times \left(\text{APPLICATION RATE} \left(\frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \times \left(\frac{\text{SEED}}{\text{BAG}} \right) \times \left(\frac{\text{BAG}}{\text{DAY}} \right) \times \left(\frac{1}{\text{BODY WEIGHT (kg)}} \right) \times 0.75 \text{ (dermal absorption)}$$

$$\text{LADD} = \text{ADD}_{\text{(inhalation \& dermal)}} \times \left(\left(\frac{\text{Days Worked}}{\text{Week}} \right) \times \left(\frac{\text{Weeks Worked}}{\text{Year}} \right) \right) \times \left(\frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right)$$

$$\text{CANCER MOE} = \frac{\text{NOAEL} (4.7 \text{ MG / KG / DAY})}{\text{LADD}}$$

b. Occupational Risk Assessment/Characterization

i. Risk from Dermal and Inhalation Exposures

HED's level of concern for difenoconazole are for MOEs below 100. Estimated MOE's are well above 100. Therefore, exposure to difenoconazole is not expected to exceed HED's level of concern. No inhalation endpoint (for any period of time) was identified by the HIARC.

ii. Risk from Post-Application Exposures

Since Dividend™ is registered solely as a commercial seed treatment product, there are no post-application exposures associated with this use.

iii. Incident Reports

Incident report data is available for difenoconazole. Two cases have been reported in OPP's Incident Data System by the registrant. They consist of instances of human exposure (in Ohio and Minnesota) which both took place in 1995. Neither case was confirmed and it is not known whether the alleged cases sought medical attention for their symptoms. One case (not wearing protective clothing) complained of pain and tingling in the arms and blurred vision. The second case complained primarily of flu-like symptoms and redness of the hands. There were no reports of exposure or illness due to difenoconazole from 1993 to 1996 among 431,684 unintentional cases reported to the nation's poison control centers participating in the Toxic Exposure Surveillance System. The California Pesticide Illness Surveillance Program had no reports of difenoconazole-related illness from 1982 through 1995. Based on lack of incidents from these three sources, no changes in labeling are recommended.

4. From Cumulative Exposure To Substances with a Common Mechanism of Toxicity:

Difenoconazole is a member of the **triazole** class of pesticides. Other members of this class include cyproconazole, fenbuconazole, propiconazole, tebuconazole, and uniconazole.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

HED does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, HED has not assumed that difenoconazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether difenoconazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenoconazole need to be modified or revoked.

DETERMINATION OF SAFETY FOR U.S. POPULATION

1. *Acute Aggregate Risk.*

From the acute dietary (food only) risk assessment, a high-end exposure estimate was calculated for the subgroup, females 13+ years. For females 13+, less than 1% of the RfD is occupied by dietary (food only). The small acute dietary % RfD calculated for females 13+ years old provides assurance that there is reasonable certainty that no harm will be caused to both females 13+ years and the pre-natal development of infants.

An acute RfD is not established for the general population including infants and children because there were no effects observed in oral toxicity studies including maternal toxicity in the developmental toxicity studies in rats and rabbits attributable to a single exposure.

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs for difenoconazole as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate acute risk assessment process.

2. *Chronic Aggregate Risk.*

Using the exposure assumptions described in this document, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of difenoconazole ranges from 2.7% for nursing infants less than one year old up to 13.7% for children (1-6 years old). Despite the potential for exposure to difenoconazole in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the RfD. HED concludes that there is a reasonable certainty that no harm will result to any subgroup of the U.S. population from chronic aggregate exposure to difenoconazole residues.

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's DWLOCs as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to DWLOCs for difenoconazole. The estimates of difenoconazole in surface and ground waters are derived from water quality

models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate chronic risk assessment process.

3. ***Short- , Intermediate-Term Aggregate Risk***

Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water plus indoor and outdoor residential uses. There are no registered residential uses at this time. Therefore, short and intermediate-term aggregate exposure risk assessments are not required.

4. ***Long-Term Aggregate Risk***

Long-term exposure is not expected based on a one time application as a seed treatment. This risk assessment is not required.

5. ***Cancer Aggregate Exposure and Risk***

In accordance with the Agency's Proposed Guidelines for Carcinogenic Risk Assessment (May 18, 1998), the HED Cancer Assessment Review Committee classified difenoconazole as a **possible human carcinogen**. The Committee recommended that a non-linear MOE approach (Memo, L. Brunsman, 9/15/98).

From the cancer dietary (food only) risk assessment, a dietary exposure estimate of was calculated for the U.S. population. The following table shows the dietary exposure and dietary cancer MOE of this population subgroup.

Subgroup	Dietary Exposures (mg/kg/day)	Cancer MOE
U.S. population	0.000558	8400

The maximum estimated concentrations of difenoconazole in surface and ground water are less than OPP's levels of concern for difenoconazole in drinking water as a contribution to cancer aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the aggregate cancer human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of difenoconazole in surface waters and ground waters to levels of concern for difenoconazole in drinking water. The estimates of difenoconazole in surface and ground waters are derived from water quality models that use conservative assumptions regarding the

pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of difenoconazole on drinking water as a part of the aggregate cancer risk assessment process.

ENDOCRINE DISRUPTOR EFFECTS

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine DISRUPTOR effects.

DETERMINATION OF SAFETY FOR INFANTS AND CHILDREN

EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the NOAEL in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

In assessing the potential for additional sensitivity of infants and children to residues of difenoconazole, HED considered data from developmental toxicity studies in the rat and rabbit and a 2-generation reproductive toxicity study in the rat. Developmental toxicity studies are designed to evaluate adverse effects on the developing fetus resulting from maternal pesticide exposure during gestation. Reproductive toxicity studies provide information relating to pre- and post-natal effects from exposure to the pesticide, information on the reproductive capability of mating animals, and data on systemic toxicity.

On 8-Sept-1998, the HIARC evaluated the chemical difenoconazole for FQPA considerations. The following discussion represents the information that was considered and the following conclusions were drawn by the HIARC.

1. Adequacy of Data:

There are acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits. There are no identified data gaps for the assessment of potential effects on offspring following *in utero* and/or postnatal exposure to difenoconazole via the minimal set of standard studies. The HIARC also determined that a

developmental neurotoxicity study is not required for difenoconazole.

2. *Susceptibility Issues:*

The toxicology data base is complete. The data provided no indication of increased susceptibility or rats or rabbits to *in utero* and/or post natal exposure to difenoconazole. In the prenatal developmental toxicity study in rats, no evidence of developmental toxicity was seen even in the presence of maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

a. **Developmental Toxicity Studies.**

- i. Rats. In the developmental study (MRID# 42090016) in rats, the maternal (systemic) NOAEL was **16 mg/kg/day**, based on decreased body weight gain and decreased food consumption at the LOAEL of **85 mg/kg/day**. The developmental (fetal) NOAEL was **85 mg/kg/day**, based on alterations in fetal ossification at the LOAEL of **171 mg/kg/day**.
- ii. Rabbits. In the developmental toxicity study (MRID# 42090017) in rabbits, the maternal (systemic) NOAEL was **25 mg/kg/day**, based on decreases in body weight gain and food consumption at the LOAEL of **75 mg/kg/day**. The developmental (pup) NOAEL was **25 mg/kg/day**, based on increases in post-implantation loss and resorptions and decreases in fetal body weight at the LOAEL of **75 mg/kg/day**.

b. **Reproductive Toxicity Studies.**

- i. Rats. In the 2-generation reproductive toxicity study (MRID# 42090018) in rats, the maternal (systemic) NOAEL was **1.25 mg/kg/day**, based on decreased maternal body weight gain at the LOAEL of **12.5 mg/kg/day**. The developmental (pup) NOAEL was **1.25 mg/kg/day**, based on decreased pup weights at day 21 at the LOAEL of **12.5 mg/kg/day**. The reproductive (pup) NOAEL was **1.25 mg/kg/day**, based on decreased pup weights at day 21 at the LEL of **12.5 mg/kg/day**.

c. **Pre- and Post-Natal Sensitivity.**

The toxicological data base for evaluating pre- and post-natal toxicity for difenoconazole is complete with respect to current data requirements. Based on the developmental and reproductive toxicity studies discussed above, for difenoconazole there does not appear to be an extra sensitivity for pre- or post-natal effects. Based on the above, HED concludes that reliable data support use of a 100-fold margin of exposure/uncertainty factor, rather than the standard 1000-fold margin/factor, to protect infants and children.

OTHER CONSIDERATIONS

Metabolism in Plants

1. The nature of the residue in plants is adequately understood. The residue of concern is difenoconazole per se, as specified in 40 CFR 180.475.

Metabolism in Animals

2. The nature of the residue in animals is adequately understood. The residue of concern is difenoconazole per se, as specified in 40 CFR 180.475.

Analytical Enforcement Methodology

3. An adequate enforcement method (Method AG-575B, MRID# 428065-04) is available to enforce established tolerances for wheat. Quantitation is by GLC using an Nitrogen/Phosphorus detector. The petitioner proposes to use this method for corn, but at this time have no method validation data available. This method has been validated for wheat, barley, and bananas. HED expects that this method would be adequate for enforcement for the proposed tolerances on corn.

Magnitude of the Residues

4. Residues of difenoconazole are not expected to exceed 0.1 ppm in/on corn, sweet (K + CWHR), corn, sweet, forage, or corn, sweet, stover as a result of this Section 18 use. **Time-limited tolerances for the residues of difenoconazole should be established at these levels.**

Magnitude of the Residues (Meat/Milk/Poultry and Eggs)

5. Secondary residues are not expected in animal commodities as associated with this Section 18 use. Meat/milk/poultry/egg tolerances have been established as a result of other difenoconazole uses.

Rotational Crop Restrictions

6. There is a 30-day plantback restriction for all rotational crops.

International Residue Limits

7. There are pending Codex MRL's for this compound in Mexico for oat, wheat, and barley. There are MRL's for this compound in Australia for carrots (0.5 ppm), potatoes (0.02 ppm), and bananas (0.5 ppm). There are no Codex Canadian residue limits established for difenoconazole on the commodities included in these Section 18 requests. Thus, harmonization is not an issue for this Section 18 action.

SUPPLEMENTAL INFORMATION

Dietary Exposure

Table 8. Residue Considerations Summary		
PARAMETER	PROPOSED USE	COMPARISON RESIDUE DATA
CHEMICAL	Difenoconazole	Difenoconazole
FORMULATION	Dividend™	Dividend™ 3FS
CROP	Sweet corn seed	Wheat
TYPE APPLICATION	seed treatment, mist-type	seed treatment
# APPLICATIONS	one	one
Maximum # seeds treated	10 million pounds	N/A
TIMING	seed treatment	seed treatment
RATE/APPLICATION	0.5 oz. (0.01 lb. ai)/100 lbs seed	10.9 g ai/100 lbs. seed (0.024 lb. ai/100 lbs. seed)
RATE/SEASON	0.5 oz. (0.01 lb. ai)/100 lbs seed	10.9 g ai/100 lbs. seed (0.024 lb. ai/100 lbs. seed)
MAXIMUM RESIDUE	N/A	< 0.05 ppm in wheat straw and hay; < 0.01 ppm in wheat grain; 0.077 ppm in wheat forage
RESTRICTIONS	Not for use in hopper boxes, planter boxes, slurry boxes, or other seed treatment applications at or immediately before planting. Not for feed, food or oil use. Green foliage may not be grazed until 55 days after planting. Do not plant any other crop other than wheat within 30 days of planting treated seeds. For terrestrial use only, do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high water mark. Do no reuse empty containers. Do not contaminate water, food, or feed by storage, disposal or cleaning of equipment.	30-day plantback restriction for all rotational crops.
RESIDUE DATA SOURCE	N/A	MRID No. 446020-01 PP#2F4107
PERFORMING LAB	N/A	Ciba Crop Protection, Greensboro, NC

ADDITIONAL INFORMATION**Animal Feedstuffs Considerations.** Not applicable.**Processed By-Products.** Not applicable.

Progress Toward Registration. Novartis has established twelve sweet corn trails using difenoconazole in order to pursue full section 3 registration for this product as a corn seed treatment. Novartis intends to analyze and submit these samples to the Agency in the fourth quarter of 1999.

Reregistration Status. Difenoconazole is not a reregistration lists chemical.

Attachment 1: DEEM Run: S. Chun, 10/19/98

cc: D.Vogel, A.Kocialski, S.Chun
RDI: M. Morrow (11/5/98), Team (11/2/98)
D. Vogel:811F:CM#2:(703)305-0874:7509C:RAB1



13544

R118899

Chemical: Difenoconazole

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128847

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